REMARKS/ARGUMENTS

Reconsideration and allowance of the pending claims is respectfully requested in light of the remarks which follow. Claims 2-6, 8, 10, 15-17, and 23-24 have been canceled. Claims 1 and 7 have been amended. Support for the amendment of claims 1 and 7 may be found, for instance, in the specification at page 43, line 18 to page 51, line 15 (Example II). Upon entry of this amendment, claims 1, 7, 9, 11-14, 18-22, and 25-30 will be pending.

Claim rejections under 35 U.S.C. § 112, first paragraph - written description

Claims 1, 4, 8-9, 11-14, 18-22, and 25-30 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

In making this rejection, the Examiner alleges that "while the specification reasonably conveys a protective antigen having the uPA recognized cleavage site selected from the group consisting of SEQ ID NO: 4, 5, and 6 in place of the native furin cleavage site, . . . there is insufficient written description encompassing a 'plasminogen activator-recognized cleavage site' because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a 'plasminogen activator-recognized cleavage site' are not set forth in the specification as filed. *See* Office Action on page 3.

As cited by the Examiner, "[a] description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to the genus . . .". (Emphasis added.) *See* Office Action at page 3, citing *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Solely in the interest of expediting prosecution, Applicants have amended claim 1 to recite, in part, a *uPA*-recognized cleavage site. Applicants respectfully submit that amended claim 1 fully meets both prongs of the test for adequate written description as set forth in the *Eli Lilly* case.

A. The specification sets forth a representative number of species falling within the scope of the genus.

As pointed out by the Examiner, the specification discloses SEQ ID NO: 4, 5, and 6 as three examples of representative uPA-recognized cleavage sites. Applicants further direct the Examiner's attention to page 18, lines 2-6, of the present specification which discloses two journal references (Ke, S.H., *et al.*, J. Biol. Chem., 272: 20456-20462 (1977) ("Ke I"); Ke, S.H., *et al.*, J. Biol. Chem., 272: 16603-16609 (1977) (Ke II"); both incorporated by reference and attached to the present amendment as Exhibits A and B, respectively) which describe the use of substrate phage display and substrate subtraction phage display experiments to identify consensus substrate sequences that are highly selective for cleavage by uPA or tPA. In particular, Ke I describes experiments using substrate phage display methods to identify substrates for uPA which are "cleaved by uPA 840-5300 times more efficiently than control peptides containing the physiological target sequence in plasminogen". *See* Ke I at page 20457, first full paragraph of column 1. Table I of Ke I shows the sequences of 91 distinct hexamer sequences that are cleaved by uPA when a phage library of random hexapeptides was screened to detect sequences cleaved by uPA. While the court in *Eli Lilly* did not set forth an absolute value for the number of sequences required to be representative of a genus, Applicants respectfully submit that a skilled artisan would find the 91 distinct sequences disclosed by Ke I, as the result of extensive library screening, to be representative of sequences comprising the genus of "uPA-recognized cleavage sites" as claimed.

B. Description of structural features common to the genus.

Furthermore, the identification of 91 distinct sequences allowed the authors of Ke I to identify structural features of a uPA cleavage consensus site. Table II of Ke I discloses eight sequences which are the most susceptible to cleavage by uPA. *See* Table II on page 20459 of Ke I. Furthermore, Ke I discusses the general characteristics of peptide sequences recognized by uPA and arrives at the general consensus sequence "SGR(S>R,K,A)X, where X represents a variety of amino acid residues but was most often alanine, glycine, serine, valine, or arginine." *See* Ke I page 20458, bridging paragraph to next page, to page 20459, end of last full paragraph

in column 1. Applicants respectfully submit that the disclosure in Ke I of key features of a consensus cleavage sequence recognized by uPA provides "structural features common to the [claimed] genus" as required by the second prong of the test set forth in *Eli Lilly*.

In light of the foregoing, Applicants respectfully request that the written description rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 8-9, 11-14, 18-22, and 25-30 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Leppla *et al.* (U.S. Patent No. 5,677,274) ("Leppla") as evidenced by Klimpel *et al.* (PNAS, 89:10277-10281 (1992)) ("Klimpel") in view of Bayley *et al.* (U.S. Patent No. 5,817,771) ("Bayley"). To the extent that this rejection applies to the amended claims, Applicants respectfully traverse.

Solely to expedite prosecution, Applicants have amended claim 1 to more closely correspond to data from Dr. Stephen H. Leppla's declaration, showing surprisingly effective results, as discussed in greater detail below.

In making this rejection, the Examiner has essentially reiterated the grounds for rejection from the previous Office Action, but has added the additional reference, Klimpel, solely for the disclosure of the site of the furin cleave site in the protective antigen (PA) protein of anthrax toxin. *See* Office Action at page 6.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations." All three elements set forth above must be present in order to establish a *prima facie* case of obviousness.

Furthermore, as stated in M.P.E.P. § 716.01(a), "[a]ffidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by

the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103." Moreover, "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness . . . of the claims at issue." M.P.E.P. § 716.02(a).

For the reasons set forth below, Applicants respectfully request reconsideration of the declaration of Dr. Stephen H. Leppla as submitted with the response to the Office Action dated August 23, 2005. Applicants submit that Dr. Leppla's declaration establishes that the Examiner has failed to establish a *prima facie* case of obviousness. Moreover, Dr. Leppla's declaration provides evidence of secondary considerations to rebut the Examiner's alleged *prima facie* case of obviousness.

A. Dr. Leppla's declaration establishes that one of ordinary skill in the art would not have a reasonable expectation of success of practicing the claimed invention if the cited references were combined.

As part of the grounds for reinstating the rejection, the Examiner has failed to credit the declaration of Dr. Leppla, a well-known authority in the field of bacterial toxins. Specifically, the Examiner states that "it is the Examiner's *opinion* that one of ordinary skill in the art would have a reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound as taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell". (Emphasis added.) *See* Office Action at page 9.

By merely stating that "there is a reasonable expectation of success in view of the references cited", with no further explanation or rebuttal of Dr. Leppla's declaration, the Examiner has provided no reasoning as to why his own opinion should be substituted for that of an expert in the field of the invention. (Emphasis in original.) *See* Office Action at page 9. Thus, Applicants submit that the Examiner has not properly considered the rebuttal evidence presented in the expert declaration.

Specifically, in contrast to the Examiner's conclusory statement, Dr. Leppla's declaration provides a specific scientific explanation of why an ordinarily skilled artisan would have no reasonable expectation of success when combining the references. To reiterate, Dr.

Leppla emphasized the importance of compatibility of the three dimensional structure of both a protease and its substrate in effecting the binding of a protease to its cleavage site on the substrate and subsequent proteolytic cleavage (*see* Declaration ¶ 7). Accordingly, the skilled artisan would not have expected the uPA cleavage site to be accessible to uPA when the cleavage site is taken out of its normal three dimensional context within plasminogen and placed into a heterologous, non-native context such as in protective antigen. Thus, Dr. Leppla states that one of skill in the art would not have expected the non-natively situated uPA cleavage site on the mutant protective antigen to come into contact with uPA (*see* Declaration ¶ 7), citing as one rationale the fact that the uPA cleavage site in the mutant protective antigen might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell (*see* Declaration ¶ 7). Accordingly, there would be no cleavage of the mutant protective antigen by uPA or delivery of a compound to the target cell (*see* Declaration ¶ 7).

In light of the foregoing, Applicants urge the Examiner to reconsider the rebuttal evidence presented in Dr. Leppla's declaration and then withdraw the rejection under 35 § U.S.C. 103(a) in light of a lack of reasonable expectation of success.

B. Dr. Leppla's declaration provides objective secondary evidence of non-obviousness

In making the rejection, the Examiner also failed to credit Dr. Leppla's declaration with respect to its showing of surprisingly effective results, stating "the Examiner recognizes that because experiments amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references these arguments are considered to be moot". *See* Office Action at page 10.

Applicants respectfully submit that the Examiner has not properly considered the data presented in Dr. Leppla's declaration as evidence of nonobviousness based on unexpectedly advantageous properties. The data presented in Dr. Leppla's declaration unequivocally demonstrates that the claimed mutant protective antigens are surprisingly effective for the delivery of a compound to tumors overexpressing uPA *in vivo* (*see* Declaration ¶ 8). When the mutant protective antigens comprising a uPA cleavage site were systemically administered to

mice bearing one of the tumor types, B16 melonoma, T241 fibrosarcoma, or Lewis lung carcinoma, all of which overexpress uPA, highly significant tumor inhibition was observed (*see* Declaration ¶ 8).

In light of the foregoing, Applicants urge the Examiner to reconsider the evidence of unexpected results presented in Dr. Leppla's declaration as evidence of nonobviousness and then withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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